

## Penicillin as an Etiologic Factor in Ectopic Pregnancy

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### SUMMARY

*Among patients observed in private practice the incidence of ectopic pregnancy trebled after the advent of penicillin therapy in the treatment of chronic pelvic inflammatory disease. In seven of eleven cases of ectopic pregnancy in a two-year period, the patients had had penicillin therapy previously. A probable explanation is that in cases in which the fallopian tube is closed by inflammation, it reopens following penicillin therapy but, because of residual damage, the ovum may not descend to the uterine cavity and is impregnated in the tube.*

IT is well known that any factor which will delay or prevent the passage of a fertilized egg into the uterine cavity may result in tubal pregnancy.<sup>2</sup> The normal tube is a highly variable, contractile organ lined with ciliated epithelium and not simply a canal which is either open or closed. The most common condition which alters tubal function is chronic inflammatory disease, notably that of gonorrheal origin, although postabortal and puerperal infections may likewise be concerned.<sup>2</sup> The role played by inflammatory disease is most apt to be a mechanical one, through narrowing or obliteration of the lumen, or through production of blind alleys as a result of agglutination of adjacent tubal folds. Peritubal inflammation with angulation or constriction produced by adhesions is another factor which may disturb normal tubal function. Aside from the purely mechanical role which inflammation may play, it may be responsible for pronounced impairment of ciliary activity and muscular peristaltic activity, with resulting retardation of the progress of the fertilized egg along a damaged but patent tube.

The clinical course of patients with infections of the female pelvis has radically changed since the advent of antibiotics, particularly penicillin. In most cases, acute salpingitis and acute postabortal infections, if treated early with penicillin, cause little or no residual damage. Thus, the incidence of sterility following these infections has been reduced considerably. The use of penicillin has also yielded very gratifying results in chronic infections of the pelvis. Several years ago the author reported results in the treatment of a series of patients with chronic endocervicitis with the intramuscular use of penicillin in oil and beeswax and later the more

refined penicillin in oil.<sup>1</sup> The results were remarkable; 94.5 per cent of patients had definite improvement. More recently the response to this treatment, while still good, has not been as dramatic. It is believed that this is because penicillin-resistant strains are developing in many patients as a result of widespread use of the drug. Since chronic endocervicitis is the most common cause of sterility<sup>3</sup> in the female it naturally follows that many patients who are infertile might become pregnant as the result of this therapy (in the author's series, 51 per cent). It is also well known that many patients with chronic cervicitis also have associated chronic parametritis and salpingo-oophoritis, which in many instances respond to some extent to the penicillin therapy. In some cases in which the tubes were closed before penicillin therapy, tubal patency was observed after treatment with the drug. Simultaneously with these observations on the effects of penicillin, the author became aware of an increasing number of cases of ectopic pregnancy among the patients observed.

As was previously mentioned, residual damage to the tubal epithelium with impairment of ciliary activity or changes in the muscularis or serosal surface of the tube may interfere with peristaltic activity, retard the progress of a fertilized egg, and lead to ectopic pregnancy. It is conceivable that improvement following penicillin therapy may result in reopening a non-patent tube while considerable residual damage remains. In such circumstances it would be possible for a sperm to traverse the length of the tube on its own power and fertilize an egg which had not descended to the uterine cavity because normal tubal peristalsis and ciliary action were lacking. With these facts in mind, the cases of ectopic pregnancy which were observed during the years 1949 and 1950 were studied.

Eleven cases of ectopic pregnancy were observed in private practice in that period. Seven of the patients had had penicillin therapy prior to the development of the ectopic pregnancy. During the two years in which the 11 cases of ectopic pregnancy occurred, 750 patients with intra-uterine pregnancy were treated. Thus the ratio of ectopic to intra-uterine pregnancy was 1:68. In reviewing two years (1940 and 1941) prior to the advent of penicillin, it was noted that there were only two cases of ectopic pregnancy as compared with 415 intra-uterine pregnancies, or a ratio of 1:207. This more closely approaches the incidence of 1:300 reported by Schumann<sup>4</sup> in 1921. In checking records of ectopic pregnancy in which operation was done by other members of the staff of the hospital used by the author, it was noted that there were four additional cases in which the patient had received penicillin therapy prior to the development of the

<sup>1</sup>Chairman's address, presented before the Section on Obstetrics and Gynecology at the 80th Annual Session of the California Medical Association, Los Angeles, May 13-16, 1951.

TABLE 1.—*Data on Patients with Ectopic Pregnancy*

Case No.	Age	Para	Gravida	Duration of Sterility	Period Between Last Penicillin and Ectopic Pregnancy	Associated Pathologic Conditions
1. ....	30	I	I	3½ years	7 weeks	Bilateral salpingo-oophoritis
2. ....	31	I	I	5 years	5 weeks	Bilateral salpingo-oophoritis
3. ....	38	I	II	9 months	12 weeks	Bilateral salpingo-oophoritis
4. ....	33	0	I	12 years	23 months	Postabortal parametritis and salpingitis
5. ....	26	I	I	?	3 weeks	Parametritis
6. ....	27	0	0	6 years	3 years	Parametritis and bilateral salpingitis
7. ....	18	0	0	8½ months	2 months	Bilateral salpingitis
8. ....	26	0	I	9 years	9 months	Bilateral salpingo-oophoritis and syphilis under treatment
9. ....	27	0	II	10 years	6 months	Right salpingo-oophoritis and arrested syphilis
10. ....	34	I	III	?	4 months	Left salpingo-oophoritis
11. ....	34	0	I	?	3 months	Bilateral salpingitis

Note: In cases 1 to 7 inclusive, operation was done by the author; in cases 8 to 11 inclusive, by other staff members in same hospital.

ectopic pregnancy and in which penicillin might have been an etiologic factor. During the two years 1940 and 1941, there were 25 patients with ectopic pregnancy operated upon at the Cedars of Lebanon Hospital, as compared with 36 in 1949 and 1950. It is interesting to note that the incidence of spontaneous abortion in patients observed in private practice was little changed. In the years 1940 and 1941 approximately one in nine pregnancies ended in spontaneous abortion, whereas during 1949 and 1950 the incidence was approximately one in ten.

#### DISCUSSION

In considering the overall picture, the author believes that the advantages of penicillin therapy in pelvic inflammatory disease considerably outweigh the disadvantages. The number of undesirable penicillin reactions has been greatly reduced with the refinements of the present-day preparations. The number of patients who have been spared oper-

ation or invalidism by penicillin therapy is gratifying. Many women who might never have conceived without the benefits of penicillin now have children. The incidence of sterility following acute salpingitis, postabortal and puerperal infections is much lower now than it was in the era before antibiotics. However, the results of the present investigation should caution physicians to be on the alert for ectopic pregnancy in patients with pelvic inflammatory disease who have received penicillin for any reason.

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#### REFERENCES

1. Krohn, L., Harris, J. M., Priver, M. S., and Fenmore, M. S.: *Am. J. Obst. and Gynec.*, 57:774-778, April 1949.
2. Novak, E.: *Gynecological and Obstetrical Pathology*, Chapter 30, pp. 437-457. W. B. Saunders Co., Philadelphia and London, 1947.
3. Reis, R. A., and Bernick, E. A.: *Role of cervix in sterility*, *Wisconsin M.J.*, 43:306-309, March 1944.
4. Schumann, E. A.: *Extra-Uterine Pregnancy*. D. Appleton and Co., New York, 1921.